PATENT SPECIFICATION (11) 1 587 638

1 587 638

(21) Application No. 23722/77 (22) Filed 3 June 1977
(23) Complete Specification filed 25 May 1978
(44) Complete Specification published 8 April 1981
(51) INT CL³ C07C 59/68; A61K 31/19
(52) Index at acceptance
C2C 220 227 22Y 238 248 257 30Y 315 31Y 332 350 364 365 366 367 36Y 38Y 449 490 500 504 50Y 623 624 628 631 634 658 661 662 669 682 699 800 802 80Y AA BT MK TC

(72) Inventor MAX SCHIBLI

(19)

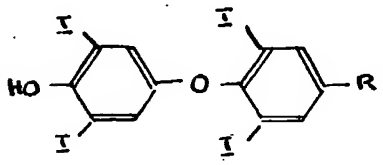
(54) IODOPHENOXYPHENYLALKENOIC ACID DERIVATIVES AND PHARMACEUTICAL PREPARATIONS CONTAINING THEM

(71) We, BEREMA S. A., a body corporate organised and existing under the laws of Switzerland, of 7 Avenue de Delay 1110-Morges, Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention concerns new medicinal preparations with a therapeutic action particularly against hypercholesterolemia, hyperlipemia (hyperlipidemie) and certain forms of obesity with overweight fat and/or cellulitis.

Many active substances are already known for the treatment of lipidic excesses and cellulitis, the most recently disclosed substances including 3,5,3'-triiodothyroacetic acid. However, this has a relatively short life since it is eliminated from the human blood in about 5 hours, and consequently has to be administered to the patient repeatedly, 4 to 5 times a day. This is a serious drawback, particularly for the patient, and especially considering that such treatments are generally of long duration (from 3 to 12 months). Research has therefore been carried out in an attempt to find substances which have a similar therapeutic action but a much longer life. This research has led to the discovery of a marked retarding action inherent in 3,5,3',5'-tetraiodothyroacetic, 3,5,3',5'-tetraiodothyropropionic and similar acids and inorganic or organic salts thereof. It takes about 15 to 18 hours to eliminate these substances from the human blood stream, which means that the number of administrations can be reduced to 1 or 2 a day at the maximum.

The invention consequently comprises a new medicinal preparation with a therapeutic action particularly against hypercholesterolemia, hyperlipemia and obesity, containing as its active substance at least one compound represented by the general formula (I).



(I)

wherein R is a carboxy substituted aliphatic radical, or a pharmaceutically acceptable salt thereof, either alone or mixed with other active substances and/or with excipients.

The R group in the compound of formula (I) is preferably an acetic, propionic or butyric acid radical.

Depending on the treatment required and the method of administration chosen, the active substance of formula (I), preferably 3,5,3',5'-tetraiodothyroacetic acid or its potassium or sodium salt, is thus used alone or mixed with other substances which may themselves be inactive or therapeutically active.

For oral administration the active substance of formula (I) is used preferably

with clofibrate and/or a choleretic cholagogue, such as divanillidene-cyclohexanone (DVCH), cyclobutyrol, sorbitol, triamcinolone, amferpramone, meprobamate, acetazolamide, alphachymotripsin, bromelains, a lipase, vitamin A, etc.

For administration by injection, the active substance of formula (I) is used preferably with hyaluronidase and/or mucopolysaccharidases, alphachymotrypsin, etc.

For rectal administration the active substance of formula (I) is used preferably with mucopolysaccharidases.

For transcutaneous administration, finally, the active substance of formula (I) is used preferably with a compound activating adenylate cyclase, such as catecholamine, e.g. adrenaline or noradenaline, bamethan, neosynephrine, salbutamol, etc. and/or with xanthine or derivatives thereof, hyaluronidase, mucopolysaccharidases, acetazolamide, etc.

The toxicity of formula (I) compounds and more particularly of 3,5,3',5'-tetraiodothyroacetic acid is low. It has been measured in mice, 5 days after a single intraperitoneal administration of the above compound in solution, diluted 50% with propanediol, and also in rats, 5 days after a single intravenous administration of the same solution as for the mice, or 5 days after a single oral administration of the active compound suspended in a carboxymethylcellulose gel. Table I shows the DL_{50} value in microgrammes per kilogramme live weight.

TABLE I

animal	administration	DL_{50} (μg/kg)
mouse	intraperitoneal	350
rat	intravenous	300
rat	oral	825

The toxicity of 3,5,3',5'-tetraiodothyroacetic acid has also been studied by observations of dogs, 4 months after oral administration of the active substance diluted with lactose, in doses of 150 μg in capsule form per kg per day. The observations were as follows: no abnormal reaction; food consumption, which was reduced for a time, returned to the same rate as that of the untreated control dogs; respiratory and cardiac rhythms normal; no disturbance of the electrocardiogram, which retains its normal basic sinusoidal movement; no discernable biological change. After autopsy a slight pallor of the thyroid glands was observed, whereas the liver, kidneys and spleen were normal, as was the weight of the heart. Nothing special was observed on histological examination of the thyroid, liver, bone medulla or on analysis of the blood formulation.

The suitability of 3,5,3',5'-tetraiodothyroacetic acid for percutaneous penetration was measured in rats. A cream containing 0.2% of compound, with part in radio-active form to provide a tracer, was applied to the animals. Rapid passage into the blood was noted, the appearance of radio-activity in the blood being observed less than 10 minutes after application.

The therapeutic effect of a treatment based on 3,5,3',5'-tetraiodothyroacetic acid on induced cholesterolemia was then studied in chickens in the following manner: 50 chickens were subjected to an atherogenic diet for 30 days, designed to create a high concentration of cholesterol in the blood; this brought the average total quantity of cholesterol (average for 50 chickens) from 125 mg per 100 ml of blood (normal quantity) to 340 mg per 100 ml (induced cholesterolemia). 30 chickens were then given 500 μg of the above active substance orally per kg per day, the other 29 chickens (1 chicken having died following the atherogenic diet) being used as a control group. The atherogenic diet was maintained both for the 19 'control' chickens and throughout the treatment of the 30 'treated' chickens. The results obtained are set out in Table II below.

TABLE II

Duration of treatment	–	36 days	57 days
Total cholesterol (in mg/100 ml)			
Control chickens	340	315	330
Treated chickens	340	145	145

The above Table shows that 3,5,3',5'-tetraiodothyroacetic acid has an effective therapeutic action against hypercholesterolemia, since the quantity of cholesterol in the blood returns to an almost normal level after 36 days of treatment, bearing in mind that the atherogenic diet is maintained.

The clinical effect of some medicinal preparations according to the invention has been studied, particularly with regard to therapeutic action against hypercholesterolemia, hyperlipemia and obesity. The conditions of administration and results obtained are described in the following examples 1 to 5:

Example 1

3,5,3',5'-tetraiodothyroacetic acid alone is administered 3 times a day at 350 μg a time to 3 men (subjects 1 to 3) and 4 women (subjects 4 to 7) of ages ranging from 35 to 52 years. The results obtained are set out in Table III.

TABLE III

Subject		1	2	3	4	5	6	7
Duration of treatment (weeks)		3	3	4	3	4	5	3
Cholesterol (mg/ml)	Before	3.40	3.50	3.90	4.15	4.2	3.20	3.80
	After	2.20	2.20	2.60	3.20	3.10	2.50	2.40
Total lipids (mg/ml)	Before	7.0	8.0	6	8.2	9	10.2	8
	After	6.0	6.0	5.4	7.9	7.5	8.0	6.5
Weight of subject (kg)	Before	71	97	84	65	62	70	48
	After	63	92	79	60	59	64	47
Height of subject (m)		1.62	1.75	1.76	1.54	1.60	1.53	1.55
Reduction in measurement (cm)								
Waist		3	5	5	7	3	7	2
Hips		4	6	5	5	4	7	3
Thighs		2	2	3	4	2	3	1

Example 2

A preparation in capsule form containing 350 μg of 3,5,3',5'-tetraiodothyroacetic acid, 25 mg of amfepramone and 100 mg of meprobamate are administered at the rate of 2 capsules a day to 4 male patients aged 45 to 55 years. The results obtained are shown in Table IV.

TABLE IV

Subject		1	2	3	4
Duration of treatment (weeks)		3	3	8	8
Cholesterol (mg/ml)	Before	3.10	4.50	4.50	3.20
	After	2.60	2.50	3.10	2.50
Total lipids (mg/ml)	Before	7.5	9.0	9.5	7.8
	After	6.5	7.5	8.2	6.0
Weight of subject (kg)	Before	72	87	81	00
	After	68	81	77	90
Height of subject (m)		1.70	1.75	1.65	1.80
Reduction in measurement (cm)					
Waist		4	6	5	8
Hips		3	5	4	6
Thighs		2	2	3	2

Example 3

A cream containing 100 ml of 3,5,3',5'-tetraiodothyroacetic acid, 15,000 TRU of mucopolysaccharidases and an excipient (e.g. containing 12 g of cetomacrogol, 5 g of lauric acid hexylester, 0.05 g of methyl p-oxybutyrate and 0.05 g of propyl p-oxybutyrate, the remainder being water) qsq 100 g, is applied locally to 5 women suffering from obesity with cellulitis. The results are summarised in Table V.

TABLE V

Subject	1	2	3	4	5
Duration of treatment (weeks)	4	6	6	6	6
Cutaneous suppleness					
Before	nil	average	nil	nil	nil
After	good	fairly good	good	fairly good	good
Orange peel effect					
Before	yes	yes	yes	yes	yes
After	improved	much improved	much improved	little improved	much improved
Reduction in measurements (cm)					
Waist	4	6	3	5	4
Hips	3	4	3	6	4
Thighs	2	3	2	4	2
Tolerance	G	G	G	G	G

NB. Improved = appearance of skin improved

Much improved = appearance of skin much improved

Little improvement = little improvement in appearance of skin

G = Good

Good tolerance is taken as meaning that no discernable side effects were found in the women to whom the above cream was applied.

Example 4

3,5,3',5'-tetraiodothyroacetic acid is applied in the form of a 0.2% solution in dilute propane diol, by ionisation (electrode — ; 15 mA), at the rate of 20 minutes twice a week, alternating with application of the cream described in Example 3.

A clear decrease in rolls of fat is observed, also a clear decrease in sub-cutaneous infiltration of the cellulitic type and hence an improvement in measurements; tolerance for the treatment is found to be excellent.

Example 5

Two subjects are treated for 8 weeks with a preparation containing 0.350 mg of 3,5,3',5'-tetraiodothyroacetic acid and 0.5 mg of triamcinolone. They show a marked decrease in weight and a simultaneous reduction in obesity as well as an improvement in biological parameters.

Example 6

A preparation in capsule form containing 0.5 mg of 3,5,3',5'-tetraiodothyroacetic acid, 200 mg of divannillidone cyclohexanone and 25000 I.U. of axerophtol acetate (vitamin A) is administered to 4 male patients at the rate of 3 capsules per day. The treatment is carried out for 2 to 3 weeks and repeated 2 to 3 times, with one week's therapeutic rest between each treatment. The results obtained are set out in Table IV.

TABLE VI

Subject		1	2	3	4
Duration of treatment (weeks)		2 × 2	2 × 3	3 × 2	2 × 3
Total cholesterol (mg/ml)	Before	3.10	3.05	2.80	3.60
	After	2.40	2.50	2.10	2.70
Total lipids: (mg/ml)	Before	6.9	6.1	6.0	7.05
	After	8	5.9	5.4	5.6

The above Examples demonstrate that, whatever embodiments and methods of administration are adopted, the medicinal preparations according to the invention are valuable therapeutic agents for the treatment of hypercholesterolemia, hyperlipemia, localised lipodystrophia and certain forms of obesity with excess weight and/or sub-cutaneous infiltration of the cellulitic type.

The following compositions A to D may further be mentioned as examples to illustrate the invention. The dosing ranges given for these compositions represent the total daily dosage.

A. *For oral administration*	*total daily dosage*
tetraiodothyroacetic acid	1 to 3 mg
and/or tetraiodothyropropionic acid	1 to 3 mg
and/or clofibrate	1 to 1.5 g
and/or cyclobutyrol	0.3 to 0.8 g
and/or DVCH	0.6 to 1 g
and/or sorbitol	3 to 5 g
and/or triamcinolone	0.05 to 2 mg
and/or amfepramone	50 to 100 mg

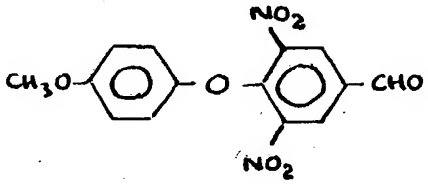
A. *For oral administration*		*total daily dosage*
	and/or meprobamate	0.05 to 0.02 g
	and/or acetazolamide	50 to 300 mg
	and/or alphachymotripsin	50 to 50,000 U.S. Hb
	and/or bromelain (extracted from sativus pineapple and comosus pineapple)	100,000 to 300,000 units
	and/or lipase	10,000 to 30,000 units of lipolytic activity
B.	*For administration by injection*	
	tetraiodothyroacetic acid	0.5 to 1.5 mg
	and/or tetraiodothyropropionic acid	0.5 to 1.5 mg
	and/or hyaluronidase	5,000 to 20,000 TRU
	and/or mucopolysaccharidases	10,000 to 20,000 TRU
	and/or alphachymotrypsine	50.000 UC. Hb
C.	*Rectal administration*	
	tetraiodothyroacetic acid	0.5 to 1.5 mg
	and/or tetraiodothyropropionic acid	0.5 to 1.5 mg
	and/or mucopolysaccharidases	10,000 to 15,000
D.	*Transcutaneous administration*	
a)	Cream, gel, ointment, liniment	doses as percentages
	tetraiodothyroacetic acid	0.1 to 0.2
	and/or tetraiodothyropropionic acid	0.1 to 0.2
	and/or adrenaline, noradrenaline, bamethan, neosynephrine, salbutanal, xanthine and xanthine derivatives. and/or hyaluronidase	5,000 to 20,000 TRU
	and/or mucopolysaccharidases	10,000 to 15,000 TRU
	and/or acetazolamine	3 to 10%
b)	solutions for ionisation	
	tetraiodoethyroacetic acid	0.05 to 0.2
	and/or tetraiodothyropropionic acid	0.05 to 0.2
	and/or mucopolysaccharidases	10,000 to 15,000 TRU

Furthermore, preparations with extensive diffusion, in the galenical form of microspheres, may be provided to make better use of the retarding action inherent in the active compounds of Formula (I).

Finally, the preparation of the active compounds of formula (I), which are used in the medicinal preparations according to the invention, will now be described with reference to the following example, which concerns the preparation of 3,5,3',5'-tetraiodothyroacetic acid.

3,5,3',5'-triiodothyroacetic and similar iodophenolic products may be prepared e.g. by the following successive reactions:

a) formation of the compound of the formula



by reacting chlorodinitrobenzaldehyde and p-methoxyphenol in the presence of $CH_3—H_2$ or of a reducing agent such as bisulfite;

b) replacement of the two nitro groups with two $—NH_2$ groups by reduction (Raney nickel) in an alcoholic medium; then diazotation of the non isolated diamine and Sandmeyer reaction in the presence of an iodine-iode solution in a sulphuric acid medium, to replace the two $—NH_2$ groups with two iodo groups;

c) formation of the corresponding acid by treatment with PCl_5 and obtaining the chlorine derivative, then treating the derivative with KCN, conversion into nitrile and hydrolysis by HI in the presence of red phosphorus;

d) iodisation by I_2 is an ammoniacal medium to provide the desired tetraiodo derivative, after recrystallisation in absolute alcohol, having a melting point of 241°C and the following spectral properties: — infra-red spectrometry (KBr pellet)

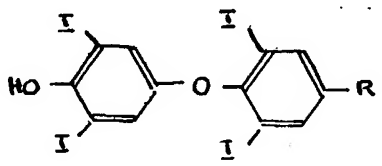
ν OH	3460 cm^{-1}
ν C=O	1708 cm^{-1}
ν C—O—C	1147 cm^{-1}

UV spectrometry
maximum absorption at 300 mm ± 1.5 ($\varepsilon^{1\%}_{1cm}$ = 59.0)
nuclear magnetic resonance
(solvent: $(CD_3)_2$ CO; s in ppm; internal reference TMS)

s	protons	appearance	integration (protons)
8.3–9.5	O*H*, COO*H*	low	2 exchangeable with D_2O
7.88	H_2 and H_6	singlet	2
7.15	H'_2 and H'_6	singlet	2
3.68	CH_2	singlet	2

WHAT WE CLAIM IS:—

1. Compounds of the formula



(I)

where R is a carboxy substituted aliphatic radical, and non-toxic, pharmaceutically acceptable salts thereof with organic or inorganic bases.

2. A compound according to claim 1, where R is $—CH_2COOH$, $—CH_2CH_2COOH$ or $—CH_2CH_2CH_2COOH$.

3. The alkali and alkaline earth metal salts of the compound claimed in claim 2.

4. A pharmaceutical preparation comprising a compound or salt according to any one of the preceding claims in admixture with a pharmaceutically acceptable carrier or diluent and/or with one or more other pharmaceutically active ingredients.

5. A preparation according to claim 4, in orally administrable form and which comprises said compound or salt in admixture with one or more of the following: a choleretic cholagogue, cyclobutyrol, sorbitol, triamcinolone, amfepramone, meprobamate, acetazolamide, alphachymotripsin, a bromelain, a lipase or Vitamin A.

6. A preparation according to claim 4, in parenterally administrable form and which comprises said compound or salt in admixture with a mucopolysacchridase, a hyaluronidase or alphachymotripsin.

7. A preparation according to claim 4 in transcutaneously administrable form and which comprises said compound or salt in admixture with a catchecholamine, bamethan, neosynephrine, salbutamol, xanthine or a xanthine derivative, hyaluronidase, a mucopolysacchridase or acetazolamide.

8. A preparation according to claim 7, comprising said compound or salt in admixture with adrenaline or noradrenaline.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 & 10 Staple Inn,
London WC1V 7RD.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1981.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.